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SPONTANEOUSLY ARISING DISEASE

Short Title: Equine Large Intestinal Fibrosis

**Idiopathic Fibrosis of the Tunica Muscularis of the Large Intestine in Five
Horses with Colic**

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Summary

Histological evidence of fibrosis affecting the outer layer of the large intestinal tunica muscularis was identified in five of 32 horses affected by colic. In three cases, foci of pale eosinophilia and vacuolation of myocytes were observed. These findings are suggestive of a degenerative and fibrotic abnormality in the outer layer of the tunica muscularis of the large intestinal smooth muscle of some horses with colic.

Keywords: horse; intestine; tunica muscularis; fibrosis

Primary disorders of the intestinal smooth muscle, including enteric myopathies and visceral myopathies, are characterized by enteric muscular abnormalities (i.e. smooth muscle fibrosis and/or vacuolation). The resultant dysfunction of the intestinal tunica muscularis can lead to intestinal pseudo-obstruction, which has been recognized in the dog (Washabau, 2003; Eastwood *et al.*, 2005), cat (Harvey *et al.*, 2005) and people (De Giorgio *et al.*, 2004a, b; Knowles *et al.*, 2004; Antonucci *et al.*, 2008). Impaired intestinal motility is recognized in a number of diseases in horses, including colonic impaction (Dabareiner and White, 1995), post-operative ileus (Blikslager *et al.*, 1994) and equine grass sickness (dysautonomia) (Doxey *et al.*, 1991). It may also be important in other conditions resulting in colic in this species.

Representative, full-thickness intestinal samples were obtained from 32 horses affected by colic, examined at Bell Equine Veterinary Clinic, Kent, UK, between January 2010 and May 2011, either as biopsy samples taken during exploratory celiotomy (26 cases) or at post-mortem examination (six cases). The sites of sampling included the large colon in 27, the small intestine in 12 and the caecum in

nine horses. Animals were affected by a variety of conditions identified commonly in equine colic, including small intestinal strangulation, large colon displacement and caecal impaction. Post-mortem samples were collected within 30 min of death and placed immediately into 10% neutral buffered formalin. In addition, samples of intestine were obtained from a 7-year-old Connemara gelding that was humanely destroyed for reasons unrelated to the gastrointestinal tract disease, as a control. Fixed tissues were processed routinely and embedded in paraffin wax. Sections (4 µm) were stained with haematoxylin and eosin (HE) and haematoxylin–Van Gieson’s stain (HVG) for collagen. The stained tissue sections were examined routinely by light microscopy. Follow-up information on the horses was obtained from the animals’ medical records and via a telephone questionnaire of the owners.

There were 16 geldings, 14 mares and two entire males, with a mean age of 18 years (range 1–29 years). Fibrosis affecting the tunica muscularis of the large intestine was identified in five horses (15.6%). Details of these horses, their clinical presentation, diagnosis, management and outcomes are summarized in Table 1. Changes were most commonly observed in the large colon (4/5 cases) and the caecum (1/5 cases), and were confined to the outer layer of the tunica muscularis. They comprised of increased fibrosis both between (interfascicular) and within (intrafascicular) occasional muscle bundles (Fig. 1), and fibrosis was confirmed with HVG staining (Fig. 2). In three cases, occasional foci of pale eosinophilia and vacuolation of myocytes, suggestive of degeneration, were observed. In addition, in one case, the muscle was infiltrated by mixed inflammatory cells (Fig. 3). Ganglion cells of myenteric and submucosal plexi appeared normal.

One of the five horses (case 3) was humanely destroyed at the time of surgery at the owner’s request. Three of the four remaining horses were alive at the time of

follow-up (between 2.75 and 3.75 years after surgery); one had been humanely destroyed due to severe colic. All three remaining horses had demonstrated at least one episode of colic during the follow-up period (one episode in case 1; two episodes in case 5; four episodes in case 2).

Although fibrosis of the submucosa of the small intestine of horses has been reported (Traub-Dargatz *et al.*, 1992; Schultheiss *et al.*, 1995; Johnson *et al.*, 1997), the authors are unaware of any previous reports of fibrosis of the smooth muscle of the intestine. There are, however, reports of neuropathies associated with intestinal dysfunction in horses, including equine grass sickness (Scholes *et al.*, 1993; Cottrell *et al.*, 1999), impactions, displacements and volvulus/torsion of the large colon (Schusser *et al.*, 1997) and chronic recurrent caecal impaction (Schusser *et al.*, 2000). Although quantitative analysis of the myenteric plexi was not undertaken in the present study, abnormalities were not identified on histopathological examination. There are three published case reports of horses with myenteric ganglionitis (Burns *et al.*, 1990; Chenier *et al.*, 2011; Blake *et al.*, 2012), one of which had vacuolation and degeneration of numerous myocytes in the outer muscular layer, similar to the changes identified in some horses in the present report. Similar vacuolar degenerative changes of the small intestinal smooth muscle have also been identified in intestinal biopsy samples taken from the cranial border of resected small intestine of horses with small intestinal strangulation (DeCeulaer *et al.*, 2011).

The aetiopathogenesis and clinical significance of the changes identified in this study remain undetermined, and, therefore, the changes are considered to represent idiopathic fibrosis. It is noteworthy that in one horse, in addition to fibrosis, the muscle was infiltrated by mixed inflammatory cells. Chronic inflammation is known to precede fibrosis in many diseases (Wynn, 2004) and it is possible that the

fibrosis identified in the intestinal tunica muscularis in these horses could be the result of previous inflammation. Degeneration and coagulation necrosis of muscle cells in the intestinal muscularis has also been described in horses with experimentally induced endotoxaemia (Oikawa *et al.*, 2007), and it is possible that the fibrosis observed in our cases was a consequence of previous endotoxin-induced muscle damage.

In the present study, four horses discharged home following surgery were affected by further bouts of colic, which in one case required humane destruction and in another case involved four episodes of colic in 3.75 years. While it is possible that the fibrosis of the tunica muscularis may have predisposed these horses to further episodes of colic, it should be recognized that recurrent colic is common following treatment of colic (Hillyer *et al.*, 2002; Scantlebury *et al.*, 2011), although the mechanisms of this are unclear.

Conflict of Interest Statement

The authors declare no conflict of interests related to the publication of this article.

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Figure Legends

Fig. 1. Case 1, large colon showing fibrosis of the interfascicular connective tissue (arrowhead) of the outer muscle layer between the muscle fascicles. HE. Bar, 500µm.

Fig. 2. Case 1, large colon showing more pronounced fibrosis of the interfascicular bundles (arrowhead) with some intrafascicular fibrosis (arrow). HVG. Bar, 500µm. Inset: Control, large colon showing the external muscle layer (flat arrowhead) with minimal interfascicular connective tissue. HVG. Bar, 500µm.

Fig. 3. Case 2, large colon showing apparent loss of smooth muscle (arrow) with increased pale eosinophilic tissue (arrowhead) in the outer muscle layer. An infiltrate of mixed inflammatory cells can be seen throughout. M, normal inner circular muscle layer. HE. Bar, 100µm. Inset: Case 2, large colon showing marked deposition of connective tissue. HVG. Bar, 100µm.